

WHAT IS CLAIMED IS:

1. A method of oxidizing a phosphite ester linkage in a nucleic acid array to a phosphate linkage, comprising contacting said phosphite ester linkage with a solution of from about 0.005 M to about 0.05 M iodine in a mixture of water and organic solvent.

2. A method of preparing a nucleic acid array on a support, wherein each nucleic acid occupies a separate known region of the support, said synthesizing comprising:

(a) activating a region of the support;

(b) attaching a nucleotide to a first region, said nucleotide having a masked reactive site linked to a protecting group;

(c) repeating steps (a) and (b) on other regions of said support whereby each of said other regions has bound thereto another nucleotide comprising a masked reactive site link to a protecting group, wherein said another nucleotide may be the same or different from that used in step (b);

(d) removing the protecting group from one of the nucleotides bound to one of the regions of the support to provide a region bearing a nucleotide having an unmasked reactive site;

(e) binding an additional nucleotide to the nucleotide with an unmasked reactive site;

(f) repeating steps (d) and (e) on regions of the support until a desired plurality of nucleic acids is synthesized, each nucleic acid occupying separate known regions of the support;

wherein said attaching and said binding are each made by covalently forming a phosphite triester linkage between said nucleotides and said unmasked reactive site and further comprising oxidizing said phosphite triester linkage to a phosphate triester linkage with a solution of from about 0.005 M to about 0.05 M iodine in an aqueous solvent mixture.

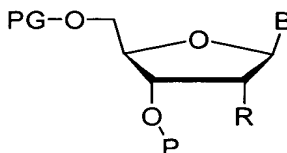
3. A method in accordance with claim 2, wherein said synthesizing comprises the sequential steps of:

a) removing a photoremoveable protecting group from at least a first area of a surface of a substrate, said surface comprising immobilized nucleotides on said

5 surface, said nucleotides capped with a photoremovable protective group, without  
6 removing a photoremoveable protecting group from at least a second area of said surface;  
7 b) simultaneously contacting said first area and said second area of said  
8 surface with a first nucleotide to couple said first nucleotide to said immobilized  
9 nucleotides in said first area, and not in said second area, said first nucleotide capped with  
10 said photoremovable protective group;  
11 c) removing a photoremoveable protecting group from at least a part of  
12 said first area of said surface and at least a part of said second area;  
13 d) simultaneously contacting said first area and said second area of said  
14 surface with a second nucleotide to couple said second nucleotide to said immobilized  
15 nucleotides in at least a part of said first area and at least a part of said second area;  
16 e) performing additional irradiating and nucleotide contacting and  
17 coupling steps so that a matrix array of at least 100 nucleic acids having different  
18 sequences is formed on said support;  
19 with the proviso that the coupling steps further comprise oxidizing an  
20 initially formed phosphite ester linkage to a phosphate ester linkage using from about  
21 0.005 M to about 0.05 M iodine in an aqueous solvent mixture.

1 4. A method in accordance with claim 3, wherein said aqueous  
2 solvent mixture comprises iodine in an amount of about 0.02 M.

1 5. A method in accordance with claim 3, wherein said nucleotides  
2 have the formula:



3 wherein

4 B is a member selected from the group consisting of natural or unnatural  
5 adenine, natural or unnatural guanine, natural or unnatural thymine,  
6 natural or unnatural cytosine, and natural or unnatural uracil;

7 R is a member selected from the group consisting of hydrogen, hydroxy,  
8 protected hydroxy, halogen and alkoxy;

9 P is a phosphoramidite group; and

10 PG is a photoremoveable protected group. .

1                   **6.**       A method in accordance with claim 5, wherein B is selected from  
2   the group consisting of adenine, guanine, cytosine and thymine and R is hydrogen.

1                   7.       A method in accordance with claim 5, wherein said array  
2 comprises at least 10 different nucleic acids.

1           8.       A method in accordance with claim 5, wherein said array  
2 comprises at least 100 different nucleic acids.

1           9.       A method in accordance with claim 5, wherein said array  
2 comprises at least 1000 different nucleic acids.

1           **10.**     A method in accordance with claim 5, wherein said array  
2     comprises at least 10,000 different nucleic acids.

1            11.     A method in accordance with claim 5, wherein said array  
2 comprises at least 100,000 different nucleic acids.

1                    **12.**     A method in accordance with claim 5, wherein each different  
2     nucleic acid is in a region having an area of less than about 1 cm<sup>2</sup>.

1                   13.     A method in accordance with claim 5, wherein each different  
2     nucleic acid is in a region having an area of less than about 1 mm<sup>2</sup>.

1                    **14.**     A method in accordance with claim 5, wherein said solution is  
2     about 0.02 M iodine in a mixture of water, pyridine and THF.

1                    **15.**        A method in accordance with claim 5, wherein B is selected from  
2        the group consisting of adenine, guanine, cytosine and thymine, R is hydrogen, and said  
3        solution is about 0.02 M iodine in a mixture of water, pyridine and THF.

1                   **16.**     A method in accordance with claim 5, wherein B is selected from  
2     the group consisting of adenine, guanine, cytosine and thymine, R is hydrogen, PG is  
3     MeNPOC and said solution is about 0.02 M iodine in a mixture of water, pyridine and  
4     THF.

1           **17.**     A method in accordance with claim 5, wherein B is selected from  
2     the group consisting of adenine, guanine, cytosine and thymine, R is hydrogen, PG is

- 3 MeNPOC, P is  $-P(OCH_2CH_2CN)N(iPr)_2$  and said solution is about 0.02 M iodine in a  
4 mixture of water, pyridine and THF.

add C<sub>1</sub>

FOSTER, E. J.